

Radiation recall dermatitis due to gemcitabine does not suggest the need to discontinue chemotherapy

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Abstract. Radiation recall is common following treatment with certain chemotherapy drugs and presents frequently as a skin reaction. With gemcitabine, such a recall phenomenon may affect internal tissues and presents itself as myositis. Although such reactions have previously been reported in the literature, whether or not to continue chemotherapy during such reactions remains controversial. We reported a case of radiation recall in a patient treated with gemcitabine and radiation therapy that presented as myositis. We were able to continue palliative chemotherapy and manage the side effects with supportive care treatment. This case report provides partial support for the continuation of chemotherapy when required even when a recall reaction is encountered.

Introduction

Radiation recall is described as inflammation occurring in previously irradiated areas which is triggered by the administration of a drug (1). It is most commonly observed when chemotherapeutic drugs, such as anthracyclines, taxanes, alkylating agents, 5-fluorouracil and capecitabine, are administered shortly after radiation, although the reaction may occur years after the completion of radiation (1,2). Radiation recall most often manifests as inflammatory reactions of the skin but may also occur in internal organs and tissues (1,2). In the event of such a reaction, the offending drug is discontinued. This case report evaluates a patient with poorly differentiated adenocarcinoma of the liver. The patient had a recall reaction in the form of myositis as a result of treatment with gemcitabine. Radiation recall induced by gemcitabine is a rare and relatively new phenomenon in the literature. Only two other cases of radiation recall in a patient being treated for cancer of the liver have been reported (3,4), and no cases exist involving primary cancer. It

has been reported that the majority of cases of radiation recall induced by gemcitabine administration involve inflammation of internal tissues and organs, which differs from the majority of reactions caused by other chemotherapeutic agents, as stated above (2). In this case report, continuing gemcitabine treatment during radiation recall was analyzed and the related current literature was evaluated.

Case report

A 50-year-old woman initially presented with right flank discomfort in January 2008. Multiple lesions were evident in the liver, and a needle biopsy confirmed the presence of poorly differentiated adenocarcinoma. Due to the fact that multiple lesions were located in multiple lobes, the patient was not a candidate for surgery and was therefore considered for radiation therapy followed by chemotherapy with palliative intent. The patient received radiation therapy for a total dose of 44.1 Gy in 15 fractions, with a biological equivalent dose of 58.5 Gy. The treatment was well tolerated, with no side effects greater than the National Cancer Institute of Canada Grade I to the radiation.

The patient was started on gemcitabine 8 weeks after completion of radiation. She received a dose of 1000 mg/m² on days 1 and 8 of a 3-week cycle. On day 8 of her fourth cycle, the patient complained of a discomfort in the previously irradiated field. An abdominal examination revealed a well-demarcated 15-cm rectangular indurated area. The overlying skin was erythematous and slightly tender to palpation. Consistent with the literature, clinical and radiological images (Figs. 1 and 2), it was determined that she presented with a radiation recall reaction induced by gemcitabine treatment, in the form of myositis.

Following consultation with the patient, the decision was made to continue with the gemcitabine treatment as the symptoms appeared to be improving in response to this treatment. The patient was then started on ibuprofen 200 to 400 mg three times a day for 6 weeks, vitamin E 400 IU two times a day and vitamin C 500 mg three times a day. She continued with two more cycles of chemotherapy and had a documented stable disease response. Subsequently, during a follow-up examination, the patient reported that the discomfort caused by the recall reaction had continued to subside. On visual

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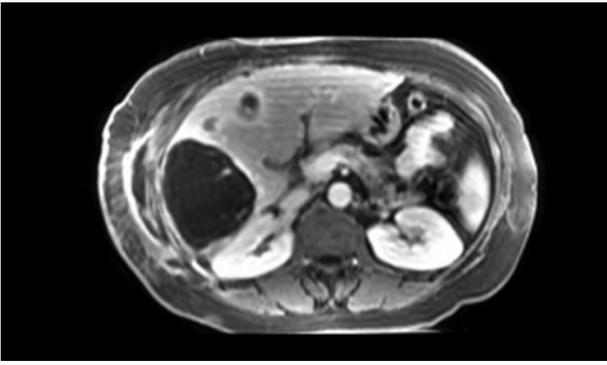


Figure 1. MRI image shows a dominant mass in the right hepatic lobe posterior segment measuring approximately 12 x 8 cm with rim enhancement. A decrease in signal intensity post contrast with mainly rim type enhancement is noted. The induration observed along the right lateral margin of the lower chest wall and abdomen of the patient is diffuse with the rim enhancement of the muscle.

examination, the reaction appeared to have decreased in size as well.

Discussion

Radiation recall occurs when an inciting agent, such as a chemotherapeutic drug, is administered after radiation. These agents most commonly produce reactions such as dermatitis or myositis, but can also produce rarely observed reactions such as optic neuritis, brainstem necrosis and erysipeloid lesions (1,5). The first reported case of radiation recall was in 1959 and was attributed to actinomycin-D (6). Although the term radiation recall and its implications are well known and various other agents have been found to cause an occurrence, less than 150 cases have been published in the literature. The majority of these cases have been reported since the turn of the century and are likely associated with the discovery and increased use of new cytotoxic agents. The exact cause or mechanism remains unknown, which is complicated by the fact that a variety of drugs have been found to induce radiation recall with different chemical, biological and metabolic characteristics. In addition, the timing of the occurrence of radiation recall has remained variable, and no particular risk factors from the patient angle have been defined.

Gemcitabine is an anti-metabolite nucleoside analog that is used against tumors such as pancreatic and lung carcinoma. Recall reactions attributed to gemcitabine are infrequently reported in the literature. A literature search of Pub Med, revealed only 28 cases since the first report in 1999 (1-5,7-21). Hird *et al* reported that gemcitabine was involved only 9 times out of 75 cases of radiation recall dermatitis since 1959 (7).

A review of the literature provides some practical insights into this phenomenon. Table I summarizes our case along with all other published radiation recall reactions related to gemcitabine. In 2004, Friedlander *et al* described that the majority of cases of radiation recall related to gemcitabine involved internal tissues and organs (2). However, our study showed that 50% of such cases involved only skin and another 18% of cases involved both skin and internal tissues. Due to the paucity of data, we were not able to correlate radiation

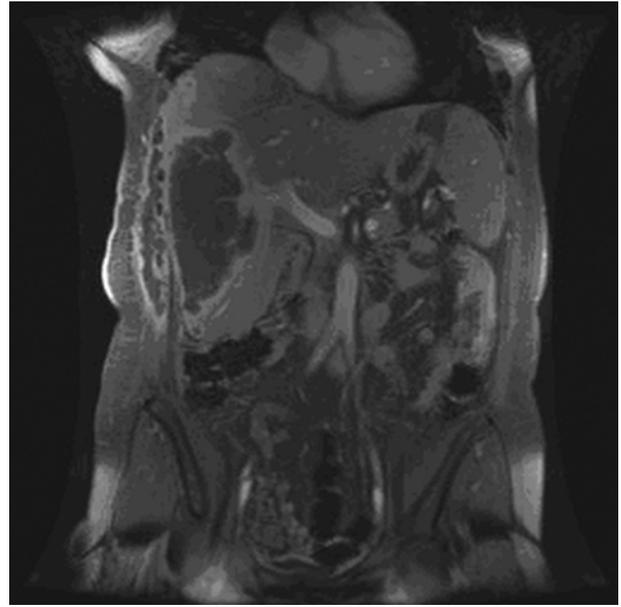


Figure 2. Coronal MRI showing the relative location of the liver lesion and muscle thickening.

dose or dose per fraction with severity or frequency. In most of the cases, radiation dose to the skin is likely to have been lower than the dose to the internal structures. Therefore, it can be suggested that the radiation dose does not appear to affect the risk of radiation recall.

In that same study, Friedlander *et al* also documented that a shorter time interval between radiation therapy and chemotherapy was correlated with recall reactions involving internal tissues (2). The averages of this interval confirm this in that the average time period for cutaneous reactions was 4 months while the average time period for reactions involving internal tissues was 2.5 months, although the medians were found to be the same at 1.5 months. The relationship between the interval from commencement of chemotherapy and the type of reaction suggests a variable sensitivity.

Another significant observation, noted by Camidge and Price in 2001, is that the risk of succumbing to a recall reaction is not affected by whether the patient receives monotherapy or if chemotherapeutic agents are administered in combination (22). We also noted that there is no significant difference between the number of gemcitabine-induced radiation recall reactions presented while the patient is receiving monotherapy or a combination treatment, nor does this appear to affect the type of reaction presented. In our case, gemcitabine administration was continued while the recall reaction was treated with conservative supportive care. Only six other studies in the literature of radiation recall induced by gemcitabine report the continuation of gemcitabine treatment, whether to maintain the current regimen or lower the dose (1,9,10,12,15). Four of these cases reported that the patients had complete improvement of their symptoms while still on gemcitabine. The other two cases reported that the symptoms improved, but then recurred following each administration. It should be noted that in one of these cases the patient received no treatment for the reaction (12). Including our case, none of the cases in which gemcitabine was continued noted an

Table I. Summary of our case and all other published radiation recall reactions related to gemcitabine.

Study	Age/ Gender	Type of cancer	Radiation dosage	Gemcitabine dosage	Other chemo drugs	Time elapsed from radiation to chemo	Time elapsed from chemo to reaction	Type of reaction	Continuation of gemcitabine	Additional treatment	Outcome
Friedlander <i>et al</i> (2)	62/M	Pancreatic	50.4 Gy in 28 fractions	1000 mg/m ² / week	No	39 days	2 months	Myositis	NR	Cortico- steroids	Full response
Fakih (8)	52/M	Pancreatic	50.4 Gy in 28 fractions	1000 mg/m ² / week	No	NR	4 months	Myositis and dermatitis	No	None	Full response
Squire <i>et al</i> (9)	54/F	Lung	30 Gy in 10 fractions	1000 mg/m ² / dose	No	1 month	2 months	Myositis	Yes	Prednisone	Symptoms reduced as prednisone increased
Saif <i>et al</i> (3)	57/M	Pancreatic	50.4 Gy in 28 fractions	150 mg/m ² as 24-h continuous infusion	Irinotecan	13 weeks	2 weeks	Antritis and duodenitis	No	Proton pump, inhibitors blood transfusion	Full response
Jeter <i>et al</i> (1)	41/F	Breast	30 Gy in 10 fractions	1000 mg/m ² / week	Herceptin	5.5 months	2 weeks	Rash	No	None	Slow improvement
Jeter <i>et al</i> (1)	59/M	NSCLC	40 Gy in 16 fractions	1000 mg/m ² / week every 2 weeks	No	3 months	3 months	Optic neuritis with subacute loss of vision	No	Dexamethasone	Improvement by MRI, no recovery of vision
Jeter <i>et al</i> (1)	79/M	NSCLC	30 Gy in 10 fractions	1 dose of 1000 mg/m ²	No	11 days	10 days	Dermatitis, typhlitis, colitis	Yes	Gel pads and bowel rest	Full response
Jeter <i>et al</i> (1)	52/F	Pancreatic	50.4 Gy in 28 fractions	1000 mg/m ² for 1 dose, then 750 mg/m ² /week	No	3 weeks	9 weeks	Dermatitis, myositis	Yes	Ibuprofen	Full response
Jeter <i>et al</i> (1)	54/M	Unknown primary	35 Gy in 14 fractions	600 mg/m ² / week	Docetaxel	1 week	7¾ months	Brainstem radionecrosis	No	Dexamethasone	Symptoms recurred after steroids lessened
Jeter <i>et al</i> (1)	63/F	Unknown primary	35 Gy in 12 fractions	1000 mg/m ² for 1 dose	No	3.4 months	3 days	Lymphangitis with erythema and edema	No	Dexamethasone	Minimal response

Table I. Continued.

Study	Age/ Gender	Type of cancer	Radiation dosage	Gemcitabine dosage	Other chemo drugs	Time elapsed from radiation to chemo	Time elapsed from chemo to reaction	Type of reaction	Continuation of gemcitabine	Additional treatment	Outcome
Tan <i>et al</i> (10)	53/F	Ovarian	25 Gy in 10 fractions	1000 mg/m ² / week	No	6 months	1 day	Dermatitis	Yes	Empirical oral antibiotics	Symptoms gradually resolved until next cycle of treatment
Tan <i>et al</i> (10)	67/M	Mesothelioma	54 Gy in 30 fractions	1 dose of 1000 mg/m ²	No	9 days	2 days	Erysiploid lesions	No	None	Full response
Schwartz <i>et al</i> (5)	67/F	Ovarian	45 Gy in 25 fractions	800 mg/m ² , then 600 mg/m ²	No	3.5 months	1 day	Dermatitis	No	Topical steroids	Quick recovery
Schwarte <i>et al</i> (11)	64/F	Esophageal	50.4 Gy in 28 fractions	1000 mg/m ² / week	Docetaxel	8 months	2 days	Pneumonitis	No	Prednisone	Recovery over 2 months
Marisavljević <i>et al</i> (12)	32/F	Stage IIB Hodgkin lymphoma	Total of 60 Gy	1250 mg/m ² / week	No	2.5 years	2 days	Dermatitis	Yes	None	Symptoms recurred after each administration
Castellano <i>et al</i> (13)	NR	NSCLC	NR	Total dose of 3000 mg/m ²	Vinorelbine	NR	2 weeks	Dermatitis and pneumonitis	No	None	Full response
Hird <i>et al</i> (7)	55/F	Metastatic breast adeno- carcinoma	20 Gy in 5 fractions to thoracic spine and 20 Gy in 5 fractions, whole brain radiation	1000 mg/m ²	Paclitaxel	10 days	2 days	Dermatitis	No	Silver sulphadiazine cream	Discoloration still apparent after 8 weeks
Bar-Sela <i>et al</i> (14)	65/M	NSCLC	45 Gy in 25 fractions	1000 mg/m ² / week	No	2 months	6 weeks	Dermatitis		i.v. antibiotics and steroids	
Welsh <i>et al</i> (15)	60/M	Transitional cell carcinoma of the bladder	45 Gy in 18 fractions	NR	Cisplatin	4 weeks	4 months	Myositis	Yes	Non-steroidal anti- inflammatory drugs and prednisone	Symptoms resolved over 6 weeks
Ganem <i>et al</i> (16)	58/F	Squamous cell carcinoma of the lung	33 Gy in 11 fractions	1000 mg/m ² / week	Cisplatin	1 month	3 months	Myositis	NR	Oral opiates, antibiotics and steroids	Progressively resolved over 3 months

Table I. Continued.

Study	Age/ Gender	Type of Cancer	Radiation dosage	Gemcitabine dosage	Other chemotherapy drugs	Time elapsed from radiation to chemo	Time elapsed from chemo to reaction	Type of reaction	Continuation of gemcitabine	Additional treatment	Outcome
Burstein <i>et al</i> (17)	41/F	Stage II breast cancer	NR	NR	No	6 months	2 weeks	Dermatitis	No	None	Slow improvement
Castellano <i>et al</i> (4)	61/M	Stage IV NSCLC	24 Gy in 8 fractions	1250 mg/m ² / week	No	4 weeks	1 week	Dermatitis	No	Dexamethasone and diphenhydramine	Completely resolved within 10 days
Fogarty <i>et al</i> (18)	65/F	Squamous cell carcinoma of the lung	36 Gy in 12 fractions	1000 mg/m ² / week	Carboplatin	4 months	6 weeks	Dermatitis and myositis	No	Oral steroids	Symptoms partially resolved
Horan <i>et al</i> (19)	58/M	Squamous cell carcinoma of the lung	24 Gy in 8 fractions	1000 mg/m ² / week	No	2 months	4 weeks	Necrosis	No	None	Symptoms gradually resolved
Monne <i>et al</i> (20)	NR	Bone metastatic breast cancer	55.2 Gy in 24 fractions	1250 mg/m ²	No	20 days	1 day	Acute dermatitis	NR	Corticosteroids and dismutase superoxide	Cutaneous and subcutaneous fibrosis was experienced
Monne <i>et al</i> (20)	NR	Lung cancer	20 Gy in 5 fractions	1250 mg/m ² / week	Cisplatin	7 days	2 months	Acute dermatitis	NR	Corticosteroids and dismutase superoxide	Cutaneous and subcutaneous fibrosis was experienced
Monne <i>et al</i> (20)	NR	Pancreatic cancer	35 Gy in 14 fractions	1250 mg/m ² / week	5-FU	12 days	3 months	Acute dermatitis	NR	Corticosteroids and dismutase superoxide	Cutaneous and subcutaneous fibrosis was experienced
Duvic <i>et al</i> (21)	NR	Cutaneous T cell lymphoma	NR	1000 mg/m ² / week		NR	NR	Skin ulceration			
Present study	50/F	Hepatocellular carcinoma	44.1 Gy in 15 fractions	1000 mg/m ² / week	Capecitabine on day 1 of each regimen	8 weeks	8 weeks	Myositis	Yes	Ibuprofen, vitamins E and C	

NSCLC, non-small cell lung cancer; NR, not recorded.

increase in symptoms or pain at any time during chemotherapy. In the case in which the symptoms recurred after each administration, the symptoms returned to their original form and did not present at a higher grade (10,12). Moreover, two of the cases in the literature documenting a discontinuation of gemcitabine treatment reported that the cancer had metastasized, leading to patient death (8,19). Clearly this is a primary consideration for the patient and health care provider when a reaction occurs. In our case, the symptoms experienced by the patient gradually improved while on gemcitabine treatment and did not worsen after administration.

Our case report, along with other similar cases in the literature, lends support to treating clinicians who decide to continue chemotherapy with gemcitabine in cases with a radiation recall reaction. Our data do not suggest that a gemcitabine recall reaction heralds a more resistant disease or greater metastatic potential. Radiation techniques or regimens do not need to be adjusted. Gemcitabine recall remains an enigmatic and rare event that should not affect primary cancer management decisions. Patients can be informed that the reaction usually resolves and does not change their prognosis.

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